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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,568	01/28/2004	Esther H. Chang	2474.0100001	8131

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EXAMINER	
HALVORSON, MARK	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
05/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,568	CHANG ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *16-18* is/are allowed.

6)☒ Claim(s) *1 and 5-15* is/are rejected.

7)☒ Claim(s) *2-4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date ~~8/8/2005~~. 8/18/2005
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 are pending.

Election/Restrictions

Applicant's election with traverse of species, one therapeutic agent, nucleic acid, wild type p53 molecule, antibody, anti-transferrin antibody in the reply filed on Feb 27, 2007 is acknowledged. The traversal is on the ground(s) that the different species are clearly related as all of the species are useful for evaluating the efficacy of a therapeutic agent that acts to induce apoptosis. Furthermore, Applicants argue that searching these groups together would not place a serious burden on the examiner. This is not found persuasive because the species, chemotherapeutic agent, radiotherapeutic agent or nucleic acid are clearly distinct types of therapies with different uses, different reagents, and different modes of action. Furthermore, there would be a serious burden on the examiner if restriction is not required because of the divergent subject matter of the different species.

Claims 1-18 are under examination.

Specification

The use of the trademarks Gemzar® and Vacutainer® has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masarenhas (US Patent No: 6,887,851, issued May 3, 2005 field Oct 4, 2002), in view of Jang et al (Int J Cancer, 2001, 173-179) and Darmon et al. (Nature, 1995, 377:446-448).

The claims are drawn to a method for evaluating the efficacy of a therapeutic agent in the body of a mammal comprising obtaining from a mammal to be treated with a therapeutic agent a sample of a body tissue in which tumor cells are present or a body fluid, wherein said tissue or fluid can contain a 17 kDa fragment of caspase 3, assaying the sample to determine the amount of cleaved 17 kDa fragment of caspase 3 present; administering said therapeutic agent to said mammal; obtaining a second sample of the body tissue or said body fluid from said mammal and assaying the second sample to determine the amount of said 17 kDa fragment of cleaved caspase 3 present; wherein an increase in the amount of said 17 kDa fragment measured in said second sample over the amount measured in the first sample correlates with apoptosis stimulation and efficacy of the therapeutic agent, wherein the amount of cleaved 17 kDa subunit in the second sample is at least 1.5 to about 2 times the amount of said cleaved subunit in the first sample.

Mascarenhas discloses that treatment of mice with mammary adenocarcinoma with insulin-like growth factor-binding protein 3 and doxorubicin increased caspase 3

activity and reduced tumor weight. (column 29 line 47-67, Table 5) compared to normal controls. Caspase 3 activity was increased by 1.5 – 2 fold over that of the control.

Mascarenhas does not disclose that treatment resulted in an increase in the cleaved 17 kDa fragment of caspase 3.

Jiang et al discloses that an increase in caspase 3 activity was the result of cleavage of the inactive proenzyme CPP-32 into the catalytically active 17 kDa protein and a 12 kDa protein. (page 176, 1st and 2nd columns). Darmon et al (Nature, 1995, 377:446-448) disclose that CPP-32 is an inactive precursor. (page 446 1st column).

One of ordinary skill in the art would have been motivated to apply Jinag et al's disclosure to Mascarenhas treatment and detection of apoptosis by caspase 3 activity because both Mascarenhas and Jiang et al detect apoptosis by examining caspase 3 activity. It would have been *prima facie* obvious to combine Mascarenhas treatment and detection of apoptosis by caspase 3 activity with Jiang et al method of measuring apoptosis by caspase 3 activity to measure caspase 3-dependent apoptosis in a different manner.

Claims 5-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masarenhas as applied to claim 1 above, and further in view of Xu et al (Mol Med, 7:723-724).

The claims are drawn to a method for evaluating the efficacy of a therapeutic agent in the body of a mammal comprising obtaining from a mammal to be treated with a therapeutic agent a sample of a body tissue in which tumor cells are present or a body fluid, wherein said tissue or fluid can contain a 17 kDa fragment of caspase 3, assaying the sample to determine the amount of cleaved 17 kDa fragment of caspase 3 present; administering said therapeutic agent to said mammal; obtaining a second sample of the body tissue or said body fluid from said mammal and assaying the second sample to determine the amount of said 17 kDa fragment of cleaved caspase 3 present; wherein an increase in the amount of said 17 kDa fragment measured in said second sample over the amount measured in the first sample correlates with apoptosis stimulation and

efficacy of the therapeutic agent, wherein said therapeutic agent comprises a comprises a DNA molecule which encodes a wild type p53 molecule, wherein said therapeutic agent is administered as a complex with a ligand-cationic liposome, , wherein said ligand comprises an anti-transferrin receptor single chain antibody fragment, wherein said antibody fragment is an scFv fragment, wherein said liposome comprises a mixture of dioleoyltrimethylammonium phosphate (DOTAP) and dioleoylphosphatidylethan-olamine (DOPE), wherein said therapeutic agent further comprises a chemotherapeutic agent or a radiotherapeutic agent.

Mascarenhas has been described supra.

Mascarenhas does not disclose a p53 gene therapy comprising administering a p53 expression plasmid cationic immunolipolex system directed by a single-chain antibody Fv fragment against the transferrin receptor, wherein the immunoliplex complex comprises a mixture of dioleoyltrimethylammonium phosphate (DOTAP) and dioleoylphosphatidylethan- olamine (DOPE) further in combination with a chemotherapeutic agent.

Xu et al disclose a systemic p53 gene therapy comprising administering a p53 expression plasmid cationic immunolipolex system directed by a single-chain antibody Fv fragment against the transferrin receptor, wherein the immunoliplex complex comprises a mixture of dioleoyltrimethylammonium phosphate (DOTAP) and dioleoylphosphatidylethan- olamine (DOPE) further in combination with docetaxel (Abstract, page 724 1st and 2nd columns).

One of ordinary skill in the art would have been motivated to apply Xu et al's systemic p53 gene therapy to Mascarenhas treatment and detection of apoptosis by caspase 3 activity because Xu et al disclose that sensitization of breast tumors to chemotherapeutic agents is due to the restoration of the apoptotic pathway (page 732, 2nd column). It would have been *prima facie* obvious to combine Mascarenhas treatment and detection of apoptosis by caspase 3 activity with Xu et al's systemic p53 gene therapy to measure apoptosis following the p53 gene therapy treatment.

Summary

Claims 1; 5-15 are rejected.

Claims 2-4 are objected to as being dependant on a rejected claim.

Claims 16-18 appear to be free of the prior art as there is no disclosure in the art that detect the 17 kDa caspase 3 fragment in the blood.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at (571) 272-0898. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark Halvorson, PhD
Patent Examiner
571-272-6539

MISOOK YU
PRIMARY EXAMINER